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09/438,989	11/12/1999	YOGESH S. SANGHVI	ISIS-4288	1111

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JOHN W CALDWELL
WOODCOCK WASHBURN KURTZ MACKIEWICZ &
NORRIS LLP
ONE LIBERTY PLACE-46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER
OWENS JR, HOWARD V

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/438,989	Applicant(s) SANGHVI ET AL.	
	Examiner Howard V Owens	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-43 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Specification

The disclosure is objected to because of the following informalities: p. 84, line 11, appears to contain the misspelled term "determin". Appropriate correction is required for this and any other spelling or grammatical errors not noted herein.

Claim Objections

In claim 23 the term "R" appears to be missing before the number 12 at the 5' position of the ribose.

Claims 22 and 43 are duplicate claims drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14 and 17-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,852,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to an oligomeric compound containing an Rp chiral phosphorothioate linked compound wherein there are substituted or non-naturally occurring nucleosides which comprise the external region of the compound. '188 does sets forth generically that the nucleoside portion is a non-naturally nucleoside, which encompasses all possible substitutions to the nucleoside moiety. The instant claims differ only with respect to claims 9, 10 and 28 set out a litany of compounds to be attached to the 2' position of the nucleoside; however, nucleoside modification whether generally or specifically at the 2' position is routine in this art.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the nucleoside portion generally or specifically at the 2' position within an oligonucleotide.

A person of ordinary skill in the art would have been motivated to modify the nucleoside portion for the art recognized purpose of either sequence specific hybridization, improving pharmacokinetic properties of the oligonucleotide or enhancing oligonucleotide resistance to degradation.

Claim Rejections - 35 USC § 112

112(2)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-8 and 15-22 applicant sets forth a substituent present in the external regions of the compound; however, applicant has not set forth what moieties or compounds encompass/define the external region.

Claims 9-14 set forth what the substituent groups are; however, the position of attachment to the external region is not set forth. Without either the position of attachment for the substituent or the compounds which define the external region, use of the terms substituent and external region are seen as vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 8, 11-13, 17-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stec et al., U.S. 5,883,237.

Claims 1-4, 7, 8, 11-13, 17-21, 23-42 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claims 22 and 43 are drawn to a pharmaceutical composition containing the compound(s) of claim 1.

The external region is any compound connected to either side of the chiral phosphorothioate (the internal region) ,i.e. a nucleoside (p. 27, lines 30-35 of specification). Substituents are defined as groups attached to a 2', 3' or 5' position of a sugar moiety as well as groups attached to the N2 or N6 position of the purine base or the N4 or C5 position of the pyrimidine (p.22, lines 9-20 of specification).

Stec anticipates the claims cited supra as it teaches oligonucleotides containing Rp or Sp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions,

nucleosides, flanking the internal region (column 7, lines 14-67). Stec teaches that these oligonucleotides may have substituted bases for both purines and pyrimidines (see columns 11-12) and may range from 1-28 nucleosides (for example, Example 24). Stec teaches that these oligonucleotides may be part of a pharmaceutical composition as well (col. 10, lines 30-57).

Claims 1-4, 6-8, 11-13 and 17-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hoke et al., U.S. 5,506,212.

Claims 1-4, 6-8, 11-13, 17-21, 23-42 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claims 22 and 43 are drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Hoke anticipates the claims cited supra as it teaches oligonucleotides containing Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region; wherein the oligonucleotides may contain up to 50 nucleosides with modified bases or sugars (columns 7-9 and claims 2 and 4). Hoke further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and stability over natural phosphodiester oligonucleotides (column 2, lines 4-20) to these oligomeric compounds. Hoke demonstrates the use of these oligonucleotides in a pharmaceutical composition as well, examples 10-12.

Claims 1-14 and 17-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cook, U.S. 5,852,188.

Claims 1-14 and 17-43 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claim 5 is drawn to the compound of claim 1 wherein there is a substituent attached to the 2' position of the nucleoside.

Claims 22 and 43 are drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Cook anticipates the claims cited supra as it teaches oligonucleotides containing Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region (column 5, line 45 - column 7); wherein the oligonucleotides contains at least 2 nucleosides (wherein the process may be repeated to obtain as many oligonucleotides as necessary- col. 16, lines 39 - 48) with modified bases or sugars in either 2' or 3' positions (columns 6-11 and claims 1-12).

Cook further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and stability to these oligomeric compounds over natural phosphodiester oligonucleotides (column 1, line 66 - column 2, line 9). Cook teaches the use of these oligonucleotides in a pharmaceutical composition as well (column 12, lines 21 - 44 and col. 11, lines 24-32).

Cook teaches modification of the nucleoside portion of these oligomeric compounds at the 2' position with a variety of groups analogous to those set forth in the instant claims 9 and 29, i.e. lower alkyl, substituted O-alkyl, substituted S-alkyl, NH-alkyl, polyalylamino, substituted silyl, etc. (col. 9, line 37 - col. line 5). Cook also teaches substitution of this 2' position with any group that improves the pharmacodynamic properties of the oligonucleotide wherein pharmacodynamic property comprises enhancing oligonucleotide resistance to degradation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-43 are rejected under 35 U.S.C. § 103 as being unpatentable over Cook, U.S. 5,852,188 in combination with Alul, U.S. Patent 5,532,130.

Claims 1-4, 6-14 and 17-21 and 24-42 are drawn to an oligomeric compound comprising a plurality of covalently bound nucleosides comprising an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking the internal region; wherein the external regions impart nuclease resistance to the oligomeric compound.

Claim 5 is drawn to the compound of claim 1 wherein there is a substituent attached to the 2' position of the nucleoside.

Claims 15 and 16 are drawn to a 2'-5' internucleoside linkage present within the oligomeric compound of claim 1.

Claims 22 and 43 are drawn to a pharmaceutical composition containing the compound(s) of claim 1.

Cook teaches oligonucleotides containing Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions, nucleosides, flanking the internal region (column 5, line 45 - column 7); wherein the oligonucleotides contains at least 2 nucleosides (wherein the process may be repeated to obtain as many oligonucleotides as necessary- col. 16, lines 39 - 48) with modified bases or sugars in either 2' or 3' positions (columns 6-11 and claims 1-12).

Cook further teaches that it is known in the art that the presence of phosphorothioates within the oligonucleotides imparts greater nuclease resistance and stability to these oligomeric compounds over natural phosphodiester oligonucleotides (column 1, line 66 - column 2, line 9). Cook teaches the use of these oligonucleotides in a pharmaceutical composition as well (column 12, lines 21 - 44 and col. 11, lines 24-32).

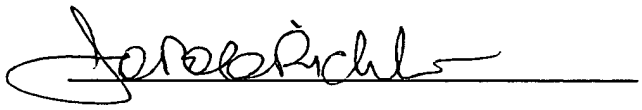
Cook teaches modification of the nucleoside portion of these oligomeric compounds at the 2' position with a variety of groups analogous to those set forth in the instant claims 9 and 29, i.e. lower alkyl, substituted O-alkyl, substituted S-alkyl, NH-alkyl, polyalylamino, substituted silyl, etc. (col. 9, line 37 - col. line 5). Cook also teaches substitution of this 2' position with any group that improves the pharmacodynamic properties of the oligonucleotide wherein pharmacodynamic property comprises enhancing oligonucleotide resistance to degradation.

Although Cook does not teach the presence of a 2', 5' internucleoside linkage within the oligomeric compound, Alul teaches that 2'-5' linkages confer resistance to both exo and endonucleolytic degradation, serve as modulators for gene expression and ; moreover that these 2'-5' linkages may be combined with 3'-5' oligomers (column 6, line 46 - col. 8) which adequately bridges the nexus between the prior art and the invention as claimed.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to incorporate a 2'-5' internucleoside linkage within an oligomer comprising a 3'-5' internucleoside linkage.

A person of ordinary skill in the art would have been motivated to incorporate a 2'-5' internucleoside linkage for the art recognized benefits of increasing nuclease resistance and regulating gene expression through sequence specific hybridization of DNA or mRNA.

Howard V. Owens
Patent Examiner
Art Unit 1623



Johann Richter, Ph.D., Esq.
Supervisory Patent Examiner
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Primary Examiner signing this action, Johann Richter can be reached on (703) 308-4532 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.